Universidade de Lisboa

Faculdade de Medicina da Universidade de Lisboa

EEG as a Prognostic Tool After Cardiac Arrest

Beatriz Faustino Guedes

Supervisor: Carla Bentes (MD, PhD)

Co-Supervisor: Manuel Manita (MD)

This thesis is submitted in partial fulfillment of the requirements for the degree of Master in Neurosciences

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Resumo

Introdução: A paragem cardiorrepiratória (PCR) é um motivo comum de internamento prolongado em Unidades de Cuidados Intensivos (UCIs) em todo o mundo. Dentro dos indivíduos que sobrevivem à admissão hospitalar, o prognóstico está sobretudo relacionado com a gravidade da lesão cerebral anóxica. É importante reconhecer desde cedo quais os doentes sem capacidade de recuperação neurológica, não só para a tomada de decisões terapêuticas, mas também para a comunicação de informações fidedignas aos familiares. Desde há muitos anos, vários preditores, clínicos e extraídos de métodos complementares de diagnóstico, têm sido utilizados para prever o prognóstico nestes doentes. Especificamente, o eletroencefalograma (EEG) tem sido um dos métodos complementares de diagnóstico mais frequentemente utilizado para auxiliar na avaliação neurológica dos doentes pós-PCR, provavelmente pelo baixo custo associado e por estar acessível na maioria dos hospitais. No entanto, tem havido alguma controvérsia sobre que características do EEG devem ser usadas para identificar com segurança um mau prognóstico neurológico devido à inconsistência nas definições de certos padrões, ao uso de protocolos de controlo de temperatura e ao uso de fármacos sedativos que alteram a atividade cerebral durante o registo do EEG. Recentemente foram propostos padrões de EEG preditores de mau prognóstico neurológico, classificados como "Altamente Malignos".

Objetivos: O objetivo primário desta tese foi avaliar se os padrões de EEG considerados "Altamente Malignos" se associam a um mau prognóstico neurológico, numa coorte de doentes diferente da previamente publicada na literatura. Os objetivos secundários foram avaliar qual o valor prognóstico de outros padrões de EEG, nomeadamente os considerados "Malignos" e "Benignos". Numa análise *Post Hoc* pretendeu-se, ainda, avaliar se os padrões de EEG considerados "Altamente Malignos" são preditores de morte, após ajuste para variáveis de confundimento e, ainda, se a presença de duas características malignas se associa a um mau prognóstico neurológico.

Métodos: Retrospetivamente, foram analisados os EEGs dos indivíduos que sofreram PCR entre janeiro de 2014 e julho de 2018, em dois hospitais universitários de Lisboa: Hospital de São José e Hospital de Santa Maria. Os EEGs foram classificados, individualmente, por três Neurologistas e Neurofisiologistas experientes segundo a mais recente terminologia de classificação de EEG nos Cuidados Intensivos da Sociedade Americana de Neurofisiologia Clínica (ACNS). Esta classificação tem em conta a atividade de base, a presença de padrões rítmicos ou periódicos e a reatividade a estímulos sonoros e nociceptivos. Apenas os EEGs realizados 48 a 100 horas pós-PCR foram incluídos na análise, uma vez que o valor prognóstico dos padrões de EEG é dependente do tempo desde a PCR até ao registo neurofisiológico. Depois de revistos e classificados, os EEGs foram divididos em três grupos segundo as suas características: um grupo "Altamente Maligno" (atividade de base suprimida, descargas periódicas contínuas numa base suprimida ou padrão de surto-supressão), um grupo "Maligno" (padrões rítmicos ou periódicos abundantes, ausência de reatividade a estímulos sonoro e nociceptivo ou reativo apenas em *SIRPIDS*, atividade de base de baixa voltagem, gradiente anterior-posterior reverso, presença de pelo menos uma crise eletrográfica e atividade de base descontínua) e um grupo "Benigno" (ausência de características altamente malignas e malignas). O prognóstico foi avaliado por um observador independente 6 meses após a PCR e classificado usando a *Cerebral Performance Categories Scale* (CPC). Foram avaliados dois grupos de resultado, um primário e numa análise *Post Hoc,* um secundário. O resultado primário foi a função neurológica avaliada pela CPC (CPC1-5) e o resultado secundário, a morte (CPC5). No resultado primário, valores de CPC1-2 foram classificados como boa recuperação neurológica (indivíduos com completa recuperação ou indivíduos com incapacidade moderada, independentes nas atividades de vida diária, com ou sem sintomas associados) e valores de CPC3-5 foram considerados um mau prognóstico neurológico (indivíduos com incapacidade grave, conscientes, mas completamente dependentes nas atividades de vida diária, em coma ou que morreram). Foi determinada a existência de uma associação entre os padrões de EEG propostos ("Altamente Maligno", "Maligno" e "Benigno") com o resultado primário e, posteriormente, calculada a associação dos padrões "Altamente Malignos" com o resultado secundário.

Foram também calculados valores de sensibilidade e de especificidade. Avaliou-se ainda se a presença de duas características malignas se associava a um mau prognóstico neurológico. Com vista à elaboração de um modelo preditor mais robusto de morte, foi construído um modelo de regressão logística multivariada, controlando a presença de um padrão de EEG "Altamente Maligno", para a idade, incapacidade prévia e realização de protocolo de controlo de temperatura. Foram avaliadas as características do modelo de predição.

Resultados: Foram incluídos 106 doentes para análise com uma idade média de 62 (±13.9) anos, 76 (71.6%) do sexo masculino. Na avaliação 6 meses pós-PCR, 79 (74.5%) doentes apresentaram um mau prognóstico neurológico e 70 (66.1%) tinham morrido. Os padrões de EEG considerados "Altamente Malignos" estiveram presentes em 37 (34.9%) doentes e todos estes apresentaram um mau prognóstico neurológico, [especificidade 100% (IC95% 87.2%-100%) e sensibilidade 46.8% (IC95% 35.5%-58.40%)]. Dos doentes com padrões "Altamente Malignos", 32 (86.5%) morreram, encontrando-se uma associação entre estes padrões e morte (p= 0.001), com valores calculados de sensibilidade e especificidade na análise bivariada de 45.7% (IC 95% 33.7%-58.1%) e 86.1% (IC 95% 70.5%-95.3%), respetivamente. Após ajustamento para variáveis de confundimento, os valores de sensibilidade e especificidade do modelo de regressão logística foram de 8.3% (IC95% 1.8%-22.5%) e 97.0% (IC95% 90.1%-99.7%), respetivamente. Para além disso, a capacidade discriminativa do modelo medida pela área abaixo da curva ROC foi pobre 0.659 (IC95% 0.554%-0.765%).

Na nossa análise, os padrões de EEG "Malignos" estiveram presentes em 39 (36.8%) doentes. Destes, 29 (74.4%) apresentaram um mau prognóstico neurológico, não sendo esta associação significativa (p=0.976). Também não se encontrou associação entre a presença de duas características malignas e um mau prognóstico neurológico (p=0.125).

Quanto aos padrões de EEG "Benignos", estes estiveram presentes em 30 (28.3%) doentes e 17 (56.7%) apresentaram uma boa recuperação neurológica. Foi encontrada associação entre estes padrões e uma boa recuperação neurológica (p<0.0001), com

valores calculados de sensibilidade e especificidade de 63.0% (IC95%42.4%-80.6%) e 83.5% (IC95%73.5%-90.9%), respetivamente.

Discussão/Conclusão: Na nossa serie, todos os doentes que 48 a 100 horas pós-PCR apresentaram um padrão de EEG "Altamente Maligno" tiveram um mau prognóstico neurológico. Para além disso, estas características neurofisiológicas foram preditores independentes de morte pós-PCR. Ademais, os padrões de EEG "Malignos" não se associaram a mau prognóstico neurológico e os padrões de EEG "Benignos" estiveram associados a uma boa recuperação neurológica 6 meses após PCR. De uma forma global, o EEG, isoladamente, mostrou-se específico, mas pouco sensível na prognosticação pós-PCR. Nos pontos fortes deste estudo incluem-se o envolvimento de dois hospitais centrais e universitários proporcionando uma discussão interpares e multidisciplinar profícua e permitindo um aumento do tamanho amostra, com influência na credibilidade dos nossos resultados. Por outro lado, o uso de terminologia recente e estandardizada na interpretação do EEG e a realização do registo do EEG numa janela de tempo específica, permitiu a comparação dos resultados com os escassos estudos previamente publicados. Algumas limitações a este estudo são também reconhecidas. Estas surgem principalmente da sua natureza retrospetiva e da não inclusão de outros biomarcadores na análise de prognóstico. Em suma, este estudo acrescenta valor ao EEG como método complementar na predição do prognóstico pós-paragem cardiorrespiratória, aumentando a evidência científica para a prática clínica corrente de requisitar um EEG nestas circunstâncias. No futuro, seria muito útil replicar este estudo de uma forma prospetiva, incluindo outros preditores clínicos, neurofisiológicos e laboratoriais e envolvendo outras Unidades de Cuidados Intensivos.

Palavras-Chave: Paragem Cardiorrespiratória, Prognóstico, EEG, Padrões Altamente Malignos, Padrões Malignos, Padrões Benignos, Preditores de prognóstico.

Abstract

Background: Cardiac arrest (CA) is a common reason for prolonged hospitalization in Intensive Care Units around the world. Among individuals who survive to hospital admission, the prognosis is mainly related to the severity of anoxic brain injury. It is important to recognize at an early stage which patients have no ability for neurological recovery, not only for therapeutic decision-making but also to facilitate the communication with patient´s family. For many years, several predictors, clinical evaluation and diagnostic tests, have been used to predict the outcome of these patients. Specifically, electroencephalogram (EEG) has been one of the most frequently used diagnostic tools to help in neurological evaluation of post-CA patients, probably because it is not excessively expensive, and it is accessible in most of hospitals. However, there is controversy about which EEG features should be used to safely identify a poor neurological outcome, due to inconsistent definitions of certain EEG patterns, the use of Target Temperature Management (TTM) and the use of sedative drugs that change the brain activity during EEG recording. Recently, specific EEG patterns, predictors of poor neurological prognosis, have been proposed, classified as “Highly Malignant” EEG patterns.

Aims: The main aim of this thesis was to evaluate if EEG patterns considered to be “Highly Malignant” are associated with a poor neurological outcome in a cohort of patients different from the one previously published. The secondary aims of this thesis were to evaluate the prognostic value of other EEG patterns, namely the “Malignant” EEG patterns and the “Benign” EEG patterns. In a *Post Hoc* analysis we also evaluate if EEG patterns considered “Highly Malignant” are predictors of death, after adjusting for confounding variables and if the presence of two malignant characteristics is associated with a poor neurological outcome.

Methods: Retrospectively, we analyzed EEGs of individuals who suffered from CA between January 2014 to July 2018 from two teaching hospitals in Lisbon: Hospital de São José and Hospital de Santa Maria. EEGs were individually classified by three experienced specialists both Neurologists and Neurophysiologists, according to the most recent standardized terminology of EEG classification in Intensive care units from

American Clinical Neurophysiology Society (ACNS). This classification takes into account the background activity, the presence of rhythmic or periodic patterns and the reactivity to sound and pain stimuli. Only EEGs performed 48 to 100 hours post-CA were included for our analysis, as the prognostic value the of the EEG patterns depends of the time since the CA occurs to the neurophysiological recordings. After review and classification, EEGs were divided into three groups according to their characteristics: a "Highly Malignant" EEG pattern group (suppressed background activity, continuous periodic discharges on a suppressed background or burst-suppression pattern), a "Malignant" EEG pattern group (abundant rhythmic or periodic patterns, absence of reactivity to sound and pain stimuli or reactive in SIRPIDS only, low voltage background activity, reverse anterior-posterior gradient, presence of at least one electrographic seizure, and discontinuous background activity) and a "Benign" EEG pattern group (absence of "Highly Malignant" and "Malignant" features). The outcome was evaluated by an independent accessor, 6 months after CA, using *Cerebral Performance Categories Scale* (CPC). Two outcome groups were evaluated: a primary outcome group and in a *Post Hoc* analyses a secondary outcome group. The primary outcome is neurological function by CPC1-5, and the secondary outcome is dead (CPC5). In our primary outcome group, CPC1-2 values were classified as good neurological recovery (individuals with complete recovery and individuals with moderate disability, but independent in daily life activities, with or without associated symptoms) and CPC3-5 values were considered a poor neurological outcome (individuals with severe disability, conscious but completely dependent on daily life, individuals in coma, or death). It was calculated the association of the proposed EEG patterns ("Highly Malignant", "Malignant" and "Benign") with the primary outcome and, posteriorly, it was calculated the association of the "Highly Malignant" patterns with the secondary outcome. It was also calculated sensitivity and specificity values. It was also evaluated if the presence of two malignant characteristics were associated with a poor neurological outcome. Aiming a more robust model of dead prediction, it was constructed a multivariate logistic regression model, controlling the presence of a "Highly Malignant" EEG pattern to age, previous incapacity, and realization of a TTM protocol. It was evaluated the characteristics of the prediction model.

Results: We included 106 patients for analysis, mean age 62 (±13.9) years, 76 (71.6%) males. In the 6-month post-CA evaluation, 79 (74.5%) patients had a poor neurological outcome and 70 (66.1%) died. EEG patterns considered to be "Highly Malignant" were present in 37 (34.9%) patients and all of them presented a poor neurological outcome, [specificity 100% (CI 95% 87.2% -100%) and sensitivity 46.8% (CI 95% 35.5% -58.40%)]. From the patients with a "Highly Malignant" EEG patterns group, 32 (86.5%) died, and an association between those patterns and dead was found (p= 0.001), with calculation of sensitivity and specificity values of 45.7% (CI95% 33.7% -58.1%) and 86.1% (CI95% 70.5% -95.3%), respectively. After adjustment for confounding variables, the sensitivity and specificity values of the regression model were 8.3% (CI95% 1.8%-22.5%) and 97.0% (CI95% 90.1% -99.7%), respectively. In addition, the discriminative capacity measured by the area under de ROC curve was poor, 0.659 (IC95% 0.554%-0.765%).

In our analysis "Malignant" EEG patterns were present in 39 (36.8%) patients, 29 (74.4%) presented a poor neurological outcome. The association between these patterns and a poor neurological outcome was not found (p= 0.976), and the association of the presence of two malignant characteristics and a poor neurological outcome was also not found (p=0.125).

Regarding "Benign" EEG patterns, these were present in 30 (28.3%) patients, and 17 (56.7%) had a good neurological recovery. An association between these EEG patterns and a good neurological recovery was found (p<0.0001), with values of sensitivity and specificity of 63.0% (CI 42.4% -80.6%), and 83.5% (CI95% 73.5% -90.9%), respectively.

Conclusion: In our cohort, all patients that 48 to 100h after cardiac arrest presented a "Highly Malignant" EEG patterns had a poor neurological outcome. Furthermore, those patterns were independent predictors of dead after CA. The "Malignant" EEG patterns were not associated with a poor neurological outcome and the "Benign" EEG patterns were associated with a good neurological recovery 6 months after cardiac arrest. Overall, EEG by itself was specific but not sensitive to post-CA prognosis. The strengths of this study include the involvement of two central and teaching hospitals providing a productive and multidisciplinary discussion and allowing for an increase of sample size,

influencing the credibility of our results. On the other hand, the use of recent and standardized terminology in EEG recording and interpretation in a specific time window allowed a comparison of results with few previously published studies.

Some limitations to this study are also recognized. These arise mainly from it retrospective nature and from the non-inclusion of other biomarkers in the prognostic analysis. In summary, this study adds value to the EEG as a test in predicting the post-cardiac arrest prognosis, increasing the scientific evidence for the current clinical practice of requesting an EEG in these circumstances. In the future, it would be very useful to replicate this study prospectively, including other clinical, neurophysiological, and laboratory predictors and involving others Intensive Care Units.

Key words: Cardiac Arrest, Outcome, EEG, Highly Malignant Patterns, Malignant Patterns, Benign Patterns, Predictors.

General Index

Tables Index

Figures Index

Acronyms and Abbreviations

ACNS - American Clinical Neurophysiology Society

AF - Ana Franco

AHA - American Heart Association

AUC - Area Under the Curve

BG - Beatriz Guedes

C- Celsius

CA- Cardiac arrest

CB - Carla Bentes

CHULC - Centro Hospitalar Universitário de Lisboa Central

CHULN - Centro Hospitalar Universitário de Lisboa Norte

CPC - *Performance Categories Scale*

CPR - cardiopulmonary resuscitation

EEG - Eletroencefalograma

GCS - Glasgow Coma Scale

IC - Intervalo de Confiança

ICUs - Intensive Care Units

LB - Luís Bento

MM - Manuel Manita

MRI - Magnetic Resonance Imaging

MRI - Magnetic Resonance Imaging

mRS - Modified Rankin Scale

MSE - Myoclonic Status Epilepticus

MSE - Myoclonic Status Epilepticus

NPV - Negative Predictive Value

PAC - Percentage Accuracy in Classification

PAC - Percentage Accuracy in classification model

PCR - Paragem Cardiorrepiratória

PD - Periodic discharges

PPV - Positive Predictive Value

RDA - Rhythmic Delta Activity

ROC - Receiver Operating Characteristics

RP - Rita Peralta

SD - Standard Deviation

SIRPIDS - Stimulus Induced Rhythmic Periodic or Ictal Discharges

SMI - Serviço de Medicina Intensiva

SSEP - Somatosensory Evoked Potentials

SW - Spike and- Wave or Sharp-and-Wave Discharge

TH -Therapeutic Hypothermia

TTM - Targeted temperature management

U/N -Unknown

UCIs - Unidades de Cuidados Intensivos

UUM - Unidade de Urgência Médica

Y - Years

Yo - Years Old

µV - Microvolts

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"It is literally true that you can succeed best and quickest by helping others to succeed." *–Napoleon Hill*

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In this study, BG is the principal investigator; CB is the senior investigator.

BG, CB, MM, RP contributed to study concept and design. MM, RP and CB were responsible for EEG interpretation and classification. AF and LB were independent observers of clinical data and outcome evaluation. BG was responsible for data collection and statistical analysis. Also, BG drafted different versions of the manuscript, finally approved by co-authors. CB and MM contributed to data analysis, interpretation of the data and critical revision of this thesis.

Scientific Board and Ethics Committee Approvals

This study was approved by both scientific and ethics committee. It was approved by the scientific committee: “Conselho Científico da FMUL” on the 19th December 2017, and by ethics committees: “Comissão de Ética para a Saúde do CHULN e do CAML” on the 23rd April 2018 and by “Comissão de Ética para a Saúde do CHULC” on the 7th May 2018.

1. Background

Cardiac Arrest (CA) is a common reason for hospital admission and prolonged hospitalization in Intensive Care Units around the word. Early prognostication of post-CA syndrome is essential both for therapeutic decision-making and communication with the patient family, but still a challenge in the clinical practice. In the next paragraphs, Epidemiology, Physiopathology, Management and Outcome prediction after Cardiac Arrest are review.

1.1. Epidemiology

CA is a common pathology and one of the leading causes of death in adults around the world, with an annual incidence of 50-110/100000 (Wnent et al., 2015). In Europe, approximately 176000 patients are admitted due to this condition yearly (Sondag et al., 2017).

Despite remarkable decrease in mortality in hospitalized patients in the last few years (Fugate et al., 2012), CA mortality is still very high (approximately 90%) (Wnent et al., 2015).

1.2. Pathophysiology

Patients who achieve return of spontaneous circulation after CA show significant morbidity and mortality, due to cerebral and cardiac dysfunction. This syndrome, called Post-CA Syndrome, comprises anoxic brain injury, post-CA myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology (Peberdy et al., 2010).

Early mortality of post-CA syndrome is related to the initial myocardial stunning and cardiogenic shock, which result in tissue hypoperfusion and development of multiple organ failure (Lemiale et al., 2013; Sandroni et al., 2016). Nevertheless, among those

who survive to first days since hospital admission, the outcome is mostly related to the severity of anoxic brain injury (Dragancea et al., 2015).

The pathophysiology of this post-anoxic brain injury is extremely complex and associated both to the initial ischemic event and to additional damages due to the restoration of blood flow. This ‘‘reperfusion injury’’, exacerbate excito-toxicity, intra-cellular acidosis, oxidative stress, mitochondrial dysfunction, neuro-inflammation and eventually induce cell death (Uchino et al., 2016).

Among all comatose patients after CA surviving to hospital admission, 40–66% never regain consciousness as a result of severe post anoxic encephalopathy (Zandbergen et al., 1998; Bernard et al., 2002).

1.3. Management

The continuous improvement in management of CA patients, such as high-quality cardiopulmonary resuscitation and early defibrillation, allowed more patients to achieve return of spontaneous circulation and to be admitted alive to hospital (Dragancea et al., 2015).

The management of these patients has been updated and recent recommendations have been published by the American Heart Association (AHA), based on an extensive evidence review process (Callaway et al., 2015). Some strategies such as cardiovascular, respiratory care and neurological care were developed and an update on therapeutic hypothermia (TH) was presented. Regarding TH, conflicting data was found (Morrison et al., 2010, Nielsen et al., 2013). New randomized controlled trials testing different target temperatures and different timings for initiation of temperature control after cardiac arrest were recognized and a variety of temperature targets were used. Following these results, it was recommended that the term targeted temperature management (TTM) should be adopted to refer both to induced hypothermia and active control of temperature at any target. Despite all conflict data, AHA recommend TTM, maintaining a constant temperature between 32°C and 36°C, in comatose (ie, without meaningful response to verbal commands) adult patients that

returned to spontaneous circulation after CA. This statement goes one step further reinforcing that there is essentially no patient for whom temperature control is contraindicated. Although, specific features of the patient may favor selection of one temperature over another for TTM. For example, higher temperatures might be preferred in patients for whom lower temperatures convey some risk, such as bleeding disorders (Watts et al., 1998; Lavinio et al., 2012) and lower temperatures might be preferred when patients have clinical features that are worsened at higher temperatures, such as seizures and cerebral edema (Guilliams et al., 2013; Corry et al., 2008; Guluma et al., 2008). This AHA recommendation, considering that all patients in whom intensive care is continued are eligible for TTM, was influenced by recent clinical trial data enrolling patients with all rhythms (ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, and asystole) also, by the rarity of adverse effects in trials, the high neurologic morbidity and mortality associated with no intervention at all and the preponderance of data suggesting that temperature is an important variable for neurologic recovery (Callaway et al., 2015).

1.4. Outcome predictors

Early identification of patients with no potential for recovery of brain functioning after CA, prevents inappropriate continuation of intensive care treatment and contributes to good communication between clinicians and patients' families. No single clinical exam finding, test or protocol that is perfect for determining neurological prognosis in all patients after cardiac arrest is available, perhaps because of the variability in patients and in the patterns of brain injury. International guidelines and scientific statements have summarized and refined the approach for estimating prognosis after cardiac arrest (Sandroni et al., 2014; Soar et al. 2015, Callaway et al., 2015).

Despite all the current diagnostic methods, only 10–20% of patients with a poor outcome can be detected reliably (Sandroni et al., 2014). This percentage indicates that post-CA syndrome prognosis remains uncertain in most patients. Consequently, these patients are treated on intensive care units (ICUs) for weeks and sometimes months. On the other hand, errors of diagnosis and suspension of therapeutic

investment (Taccone et al., 2015) can occur, even when a multimodal prognostic approach is initiated 72 hours after cardiac arrest and neurological function evaluation >48h is recommended (Sandroni et al., 2014).

In the next paragraphs, predictors of post-CA syndrome poor outcome a review including patients´ characteristics, circumstantial factors associated with CA and factors based on clinical and complementary evaluation.

1.4.1. Patient´s characteristics

Predictors of a poor outcome related with patient´s characteristics were previously identified and include: older age, higher body mass index, higher initial temperature and previous history of alcoholism (Kjaergaard et al., 2015; Hoydenes et al., 2016; Winther-Jensen et al., 2015).

1.4.2. Circumstances of CA

Predictors regarding the circumstances associated with CA occurrence include: collapse at start of Cardiopulmonary Resuscitation (CPR), time from collapse to return of spontaneous circulation, presence of shockable rhythms (ventricular tachycardia and ventricular fibrillation), bystander CPR, lactate levels, longer duration of low flow and treatment with adrenaline (Wibrandt et al., 2015; Hollenberg et al., 2008; Fugate et al., 2010; Lemiale et al., 2013; Sasson et al., 2010; Lin et al., 2014).

1.4.3. Clinical evaluation

Neurological examination predictors included: absence of corneal and pupillary reflexes and absence of motor response at pain stimulation (Glasgow Coma Scale motor score=1) (Nielsen et al., 2009; Larsen et al., 1993; Herlitz et al., 2003; Adrie et al., 2006; Herlitz et al., 2005; Hollenberg et al., 2008).

1.4.3.1. Myoclonic Status Epilepticus

The presence of early Myoclonic Status Epilepticus (MSE) has been classically associated with poor prognosis post-CA syndrome. Patients with MSE have prolonged, frequent, spontaneous myoclonic jerks that should be distinguished from generalized tonic clonic seizures and from the Lance-Adams syndrome, a rare post anoxic condition characterized by later onset usually with intention myoclonus (Bigham et al., 2018).

A major development in post-CA prognostication was the recognition that there are different categories of post-cardiac arrest myoclonus and that some patients with MSE may have good outcome (Callaway, 2018). In fact, a recent study describing myoclonic seizures in 29% of comatose patients, during the first 7 days after CA, showed that seizures were not reliable predictors of poor outcome, with a false positive rate of 4.3% (Lybeck et al., 2017). Another study, using video-EEG in 43 patients, delineated three clinical appearances of myoclonus and only one of which portended no awakening (Mikhaeil-Demo et al., 2017). These authors divided myoclonus in 3 types: type 1: distal, asynchronous, variable; type 2: axial or axial and distal, asynchronous, variable; and type 3: axial, synchronous, and stereotyped. According to these authors' results myoclonus type 1 and 2 could indicate a tendency towards better outcomes compared with type 3 (associated with poor outcome). Thus, careful clinical description of myoclonus is important.

The benign forms of myoclonus may be early Lance–Adams syndrome (Aicua Rapun et al., 2017). These authors reported this syndrome in 1.5% of cases with myoclonus and these patients awakened 3–23 days post-CA.

Other important finding was described in a series of 401 comatose patients in which EEG patterns could distinguish malignant myoclonus from early Lance-Adams variety (Elmer et al., 2016). They divided EEG patterns in 2 types: Pattern 1, burst-suppression background with high amplitude polyspikes in lockstep with myoclonic jerks; and Pattern 2, continuous background with narrow, vertex spike-wave discharges in lockstep with myoclonic jerks. No patient with EEG Pattern 1, other EEG feature (excluding pattern 2) or subcortical myoclonus had a favorable outcome. By contrast, 4 of 8 patients (50%) with EEG Pattern 2 survived, and 4 of 4 (100%) survivors had

favorable outcomes, despite remaining comatose for 1 to 2 weeks post-CA. It was also proposed in this study that brief neuromuscular blockade could be necessary to accurately determine the EEG pattern in patients with myoclonus (Newey et al., 2017).

Taken together, this data suggests that the MSE can still be considered a poor prognostic sign but is not as reliable as once thought. Clinicians should carefully clinically and neurophysiologically phenotype myoclonus as part of the prognostic evaluation of post-CA syndrome (Callaway, 2018; Bigham et al., 2018).

1.4.4. Diagnostic Tests

Regarding diagnostic tests, none is perfect in determining neurological prognosis for all patients after cardiac arrest. Consequently, diagnostic test results should always be associated with clinical evaluation.

International guidelines and scientific statements have summarized and refined the approach for estimating prognosis after CA (Sandroni et al, 2014; Soar et al., 2015; Oddo et al. 2016; Callaway, 2018). A recent review found that the most specific tests that can be used, associated with clinical findings, include: electroencephalography (EEG), somatosensory evoked potentials (SSEP), computed tomography (CT) scans, magnetic resonance imaging (MRI), and blood levels of various peptides released from brain tissue (Callaway, 2018).

1.4.4.1. Eletroencefalogram (EEG)

EEG is one of the complementary diagnostic methods that has been routinely used for outcome prediction of post-CA patients (Hockaday et al., 1965; Synek et al. 1988; Young et al., 1997). Currently, it is thought that this is the diagnostic tool most commonly used to support neurological evaluation, probably because it is not excessively expensive, and it is accessible in most of hospitals (Friberg et al., 2015).

EEG activity mainly reflects cortical synaptic activity (van Putten et al., 2014). Since cortical synaptic activity is very sensitive to the effects of hypoxia, the EEG is sensitive

to detection of hypoxia induced cerebral damage (Hofmeijer and van Putten, 2012). However, the specificity of pathological EEG activity for reliable prediction of poor outcome has long been uncertain (Sandroni et al. 2014).

Despite its widespread use, in 2006, the American Academy of Neurology Guidelines did not include EEG as a prognostic tool in post-CA. In fact, the scientific evidence for its accuracy was low by that time (Wijdickset al., 2006). Since then, several studies have been published bringing new evidence about the role of the EEG in the prognosis of these patients (Hofmeijer et al., 2011; Sivaraju et al. 2015, Tjepkema-Cloostermans et al., 2015, Crepeau et al., 2013).

Previously, it was described by several authors that in patients treated with hypothermia, the absence of EEG reactivity was always associated with an unfavorable outcome (Crepeau et al., 2013, Rossetti et al., 2014). However, there is some disagreement, probably due to the existence of confounding factors. Also, another study revealed that three patients without EEG reactivity after rewarming had a favorable outcome (Bouwes et al., 2012). Furthermore, it has been demonstrated that agreement in EEG interpretation is only fair for “EEG reactivity”, even among experts (Westhall et al., 2015).

In 2014, a European Advisory Statement was published by the European Resuscitation Council and European Society of Intensive Care Medicine. The authors aimed to collect all prognostication data for patients after CA (Sandroni et al., 2014). This statement report that the absence of EEG reactivity to external stimuli, the presence of a burst-suppression pattern or a status epilepticus ≥72h after return of spontaneous circulation is predictive of an unfavorable outcome in post-CA patients. However, it was advised to use these findings in combination with other predictors, since these patterns were not standardized between different centers and the evidence was limited to some studies. It was also recommended that the low amplitude of the EEG should not be used to predict an unfavorable outcome due to limited evidence, the risk of interference by hypothermia, ongoing sedation or technical factors during EEG recording. Other recommendation was against using the burst-suppression pattern for prognosis during the first 24-36 hours after return of spontaneous circulation or during

hypothermia in these patients, due to the interference of ongoing sedation. Nevertheless, this European Advisory Statement concluded that continuous or intermittent EEG recording during hypothermia and after rewarming was useful to assess the level of consciousness and myoclonus, which may be masked by prolonged sedation and neuromuscular dysfunction. In fact, EEG is the only diagnostic test capable to detect non-convulsive seizures, which may occur in about one-quarter of post-CA coma survivors (Sandroni et al., 2014).

The same authors reported that definitions for certain EEG patterns were generally inconsistent between studies, especially for burst-suppression patterns, and that there was no strong evidence on the predictive value of EEG in the prognosis of post-CA patients. They also advised that the EEG terminology for intensive care patients by the American Clinical Neurophysiology Society (ACNS) should be used (Hirsch et al., 2013), in future studies to increase interobserver agreement.

This ACNS terminology (Hirsch et al., 2013) characterizes both rhythmic and periodic patterns as well as background activity. Patterns are described based on their location (main term 1) and type of recurring discharges (main term 2). The three main pattern types include: recurring discharges of relatively uniform morphology and are divided into periodic discharges (PD); rhythmic delta activity (RDA); and spike and wave or sharp-and-wave discharge (SW). In PDs, the discharges occur at nearly regular intervals with a clearly defined inter-discharge interval, whereas in RDA there is no intervening inter-discharge interval. The SW discharges include spikes, polyspikes, or sharp waves, immediately followed by a slow wave in a regularly repeating and alternating manner (e.g., spike-wave, spike-wave, spike-wave). Multiple modifiers can be used to characterize other EEG features of the pattern of interest. The interrater agreement (IRA) for describing these patterns is nearly perfect for main terms 1 and 2, moderate or substantial for most modifiers, and fair for evolution according (Gaspard et al., 2014).

Recently, studies using this terminology for prognostic classification of EEGs in post-CA patients have been published (Sivaraju et al., 2015; Søholmet al., 2014; Westhall et al., 2016; Spalletti et al., 2016).

Another important highlight is that the prognostic value of certain EEG patterns is dependent to the time of the EEG recording. Pathophysiology of post CA syndrome, the use of intensive sedation and hypothermia, can account for this dependency (Sivaraju et al., 2015; Callaway, 2018). In fact, within 10-40 seconds after circulatory arrest, the EEG becomes isolectric reflecting massive cortical synaptic arrest (Hofmeijer and van Putten 2012).

Recently, a very important multicenter research aimed to identify reliable predictors of poor neurological outcome, using ACNS terminology in a specific lime locked window (2-4 days after CA) (Hisrch et al. 2013). They classify EEGs of 103 patients, after rewarming, and divided them into 3 groups: a "Highly Malignant" EEG pattern group, a "Malignant" EEG pattern group, and a "Benign" EEG pattern group. This study concluded that the “Highly Malignant” EEG pattern group (Burst-Suppression, Suppressed Background and Continuous Periodic Discharges), safely predict an unfavorable outcome in half of the patients, with no false positives (specificity 100%, 50% sensitivity) and a single malignant trait does not predict an unfavorable outcome (Westhall et al., 2016). This study encourages further studies in different cohorts with similar protocols so that these patterns can be reliably included in a multimodal prognostic algorithm.

Despite all the research in this field, a recent review (Oddo et al., 2017) reports that there is still no evidence on the prognostic value of EEG in post-CA patients, although it is still the most widely used diagnostic tool in these patients both to detect subclinical seizures and to assess prognosis. This review states that there is a need for evidence-based consensus on predictive EEG patterns of favorable and unfavorable outcome in post-CA patients.

2. Research question and aims

2.1- Research questions

1. Are “Highly Malignant” EEG patterns associated with a poor neurological outcome in post-CA patients, as it was proposed by Westhall and collaborators?
2. Are “Malignant” EEG patterns associated with a poor neurological outcome?
3. Are “Benign” EEG patterns associated with a good neurological outcome?

   In *Post hoc* Analysis;

4. Are “Highly Malignant” EEG patterns associated with death even after adjustment for confounding features?
5. Are more than 2 combined “Malignant” EEG features associated with poor neurological outcome?

2.2. Aims

The main aim was to determine if “Highly Malignant” EEG patterns are associated with a poor neurological outcome of post-CA patients.

The secondary aim was to determine if “Malignant” and “Benign” EEG patterns have prognostic value in post-CA patients.

In a Post hoc analyze we aim to determine if “Highly Malignant” EEG patterns were independent predictors of death and observe if more than 2 combined “Malignant” EEG features are associated with poor neurological outcome.

3- Methodology

3.1. Ethical approval

This study was approved by the ethics committees from two hospitals in Lisbon, Portugal: Centro Hospitalar Universitário de Lisboa Central (CHULC) and Centro Hospitalar Universitário de Lisboa Norte (CHULN).

3.2. Study design and data collection

This study is a retrospective cohort study. Data was collected between September 2018 and January 2019 and it concerns patients who suffered from Cardiac Arrest between January 2014 and August 2018. These patients were admitted in two intensive care units (ICU), “Unidade de Urgência Médica” (UUM) and “Serviço de Medicina Intensiva” (SMI) in their Portuguese designation, located in two teaching hospitals in Lisbon: “Hospital de São José” (CHULC) and “Hospital de Santa Maria” (CHULN), respectively. The next figure (Figure 1) represents the data collection process.

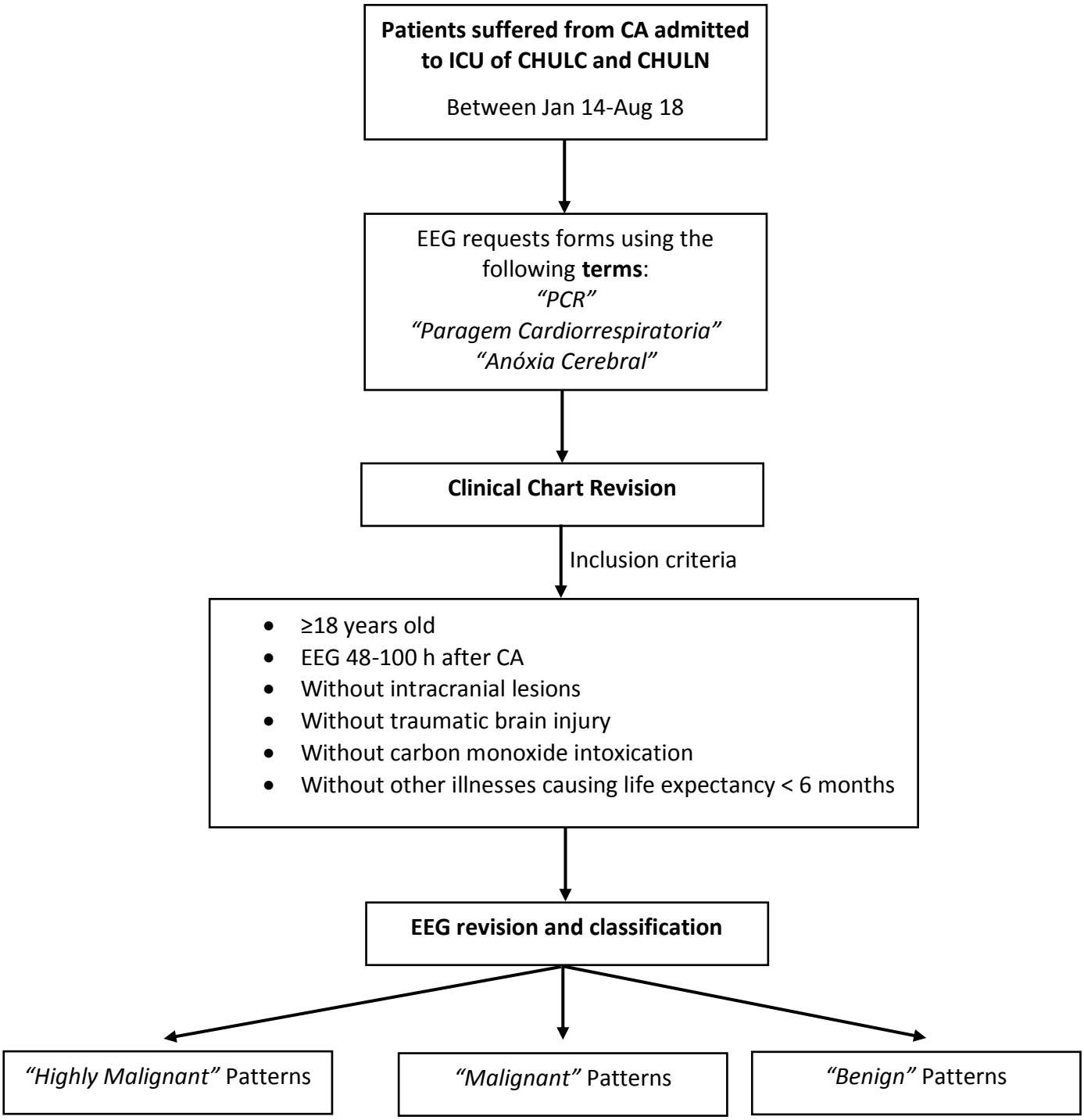

Figure 1. Study Flow Chart

3.3. Protocols of Cardiac Arrest management

Both hospitals provide to all patients, cardiovascular, respiratory and neurological care, including similar Target Temperature Management (TTM) protocols parameters. These are performed at a target temperature of 33°C and following 2015 AHA recommendations (Callaway et al., 2015), a TTM between 33°C and 36°C, depending on specific patients´ characteristics, with 24 hours maintenance, and controlled normothermia in the 72 hours after return of spontaneous circulation.

3.4. Patients´ selection (Inclusion and Exclusion criteria)

All patients were selected through a visual search of EEG request forms. To be included, one or more of the following terms had to appear in the request forms: “Paragem cardiorrespiratória”, “PCR” or “Anóxia Cerebral”.

Our protocol included all adult patients (age ≥ 18 years old) with EEG recordings completed between 48-100 hours after CA, and excluded patients who suffered from intracranial lesions, traumatic brain injury, carbon monoxide intoxication or patients with life expectancy of less than six months.

3.5. Clinical variables

A few variables from the patients´ charts related with clinical evaluation were collected for a better characterization of our cohort. Some of these variables are known to be outcome predictors of post-CA patients, as it was described in the literature review of this thesis. The variables were available on the patients´ charts and were collected by an investigator blinded to the patient´s outcome (BG).

3.5.1. Gender

Gender was defined as a dichotomous variable: masculine and feminine.

3.5.2. Age at time of CA

Age at time of CA was defined as a continuous and as a dichotomous variable: less than 50 years old (<50 yo) and more or equal than 50 years old (≥50 yo).

3.5.3. Previous Modified Rankin-Scale (mRS)

The Modified Rankin Scale (mRS) has been used as a measurement of global disability in stroke, brain injury, and neurosurgical patients (Van Swieten et al., 1988; Schaefer et al., 2004; Rabinstein et al., 2004).

The mRS is somewhat similar to the CPC (Jennet et al., 1975), though more focused on functional domains, and can also be determined using chart review (Banks et al., 2007). Its six categories are:

- **0** - no symptoms at all;
- **1**- no significant disability despite symptoms, able to carry out all usual duties and activities;
- **2** - slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance;
- **3** - moderate disability, requiring some help, but able to walk without assistance;
- **4** - moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance;
- **5**- severe disability, bedridden, incontinent and requiring constant nursing care and attention;
- **6**- dead.

This variable was accessed through the review of the patients´ charts and it concerns dependence prior to CA. It was defined as a dichotomous variable: independent (mRS 0-2) and dependent (mRS ≥3) (Bonita et al., 1988).

3.5.4. Cardiac Arrest location

This variable concerns the place where the CA occurred.

It is defined as a dichotomous variable: in-hospital CA (emergency services, intensive care units, operating room, ward, waiting room) and out-hospital CA (home, street, shopping center, etc.).

3.5.5. Cardiac Arrest cause

CA cause is defined as a categorical variable. It was accessed through the patient´s charts. The CA causes were divided into the following categories: acute myocardial infarction, Aortic Stenosis, Acute Pulmonary Edema, Disritmia, Hemorrhagic Shock, Pulmonary Embolism, Hypoxemia, Myocardiopathy and Myocarditis. When the information was not available (or reported as unknown) in the patient´s chart, it was reported as Unknown (U/N) in this study.

3.5.6. Target Temperature Management (TTM)

The information about this variable was accessed in a specific database kept by each ICU.

It is defined as a dichotomous variable: “performed”, corresponding to patients who followed this treatment protocol, and “not performed”, corresponding to patients who did not followed this treatment protocol.

A subcategory was defined from the “performed” category: “performed at 33^{o}C”, which include the patients with a Target Temperature of 33^{o}C and “performed at 36^{o}C”, which includes patients with a Target Temperature of 36^{o}C.

3.5.7. Glasgow Coma Scale (GCS)

The information regarding this variable was accessed in a specific database kept by each intensive care unit.

The Glasgow Coma Scale (GCS) is a neurological scale which aims to provide a reliable and objective way of recording the consciousness level of the patient in response to defined stimuli. Eye opening, verbal response and motor response are evaluated (Teasdale et al., 1974). The score is determined by the sum of the score in each of the 3 categories, with a maximum score of 15 and a minimum score of 3. A minimum score of 3 indicates deep coma or a brain-dead state, the maximum score of 15 indicates a fully awake patient (the original maximum was 14, but the score has since been modified). The acronym stands for both Glasgow Coma Scale (individual components) and Score (total).

We evaluated the GCS 72 hours post-CA and scored it as the total score. This variable was defined a dichotomous variable: GCS=3 which included patients with a GCS equal to 3, and GCS>3 which included the patients with a GCS greater than 3.

3.5.8. Time between CA and EEG

It was possible to collect the data for this variable through the patients' charts, which indicates the day, and time when the CA occurred, as well as the day and time of EEG recording. It was measured in hours and as a continuous variable.

3.5.9. Sedation

Sedation was defined as the ongoing infusion of any sedative or anesthetic drug: Midazolam, Fentanyl or Propofol during EEG recording.

This variable was defined as a dichotomous variable: "presence of sedation", which included the patients who were under infusion of sedative/anesthetic drugs during

EEG recording, and “not present” which included the patients who did not receive sedative/anesthetic drugs during EEG recording.

3.6. EEG recordings

All the EEG recordings included in this study were done in *a Nihon Kohden EEG digital System* (DMS) (CHLN) or in a *Micromed EEG digital System* (System PLUS EVOLUTION) (CHLC). The recordings were performed according to each laboratory´s protocol for recording EEG in intensive care units. However, all recordings used a minimum of 21 electrodes, and each EEG was recorded for at least 20 minutes and includes background reactivity testing both for sound and nociceptive stimuli.

3.7. EEG analysis

The EEG analysis and report of the EEG were performed by three EEG experts (MM, CB and RP), both resident Neurologists and Neurophysiologists in the two hospitals. The EEG classification was done using the American Clinical Neurophysiology Society (ACNS) Standardized Critical Care EEG terminology (Hirsch et al. 2013). The analysis was done individually. Interrater agreement was not calculated.

The EEG reports were divided in three groups as proposed by Westhall and collaborators in 2016. Characteristics of each pattern group are described below.

3.7.1. “Highly Malignant” EEG pattern group

- Suppressed background (<10 μV) without Periodic Discharges;
- Suppressed background (<10 μV) with Continuous (>90% of recording) Periodic Discharges;
- Burst-suppression background (with or without Periodic Discharges) with suppression periods (<10 μV) constituting >50% of the recording.

3.7.2. "Malignant" EEG pattern group

- Periodic or rhythmic patterns: Abundant Periodic Discharges (>50% of recording);
- Abundant Rhythmic Polyspike, Spike, Sharp-and-wave (>50% of recording);
- Unequivocal electrographic seizure (at least one);
- Discontinuous background with suppression periods (<10 μV) constituting >10% of the recording;
- Low voltage background (most activity <20 μV);
- Reversed anterior-posterior gradient.

3.7.3. "Benign" EEG pattern group

- Absence of all "Highly Malignant" and malignant features stated above.

3.8. Outcome measurement

The outcome was accessed 180 days after cardiac arrest by two blinded investigators to the patient's EEG and clinical variables (LB and AF).

The outcome was accessed using the Cerebral Performance Category scale (CPC). This scale is the traditional standard outcome measure for cardiac arrest survivors (Sandroni et al., 2013), and can be easily determined through chart review (Jennet et al., 1975; Cummins et al., 1991).

This scale is divided in five categories related with neurological outcome:

- **CPC1** - full recovery;
- **CPC2** - moderate disability: able to work at least part-time, and independent for activities of daily living, with or without neurological manifestations such as hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes;
- **CPC3 -** severe disability: conscious, but fully dependent for daily support because of severely impaired cognitive function;

- **CPC4** - comatose or in a persistent vegetative state;
- **CPC5** - dead.

3.8.1. Primary outcome

The primary outcome was neurological function. This is defined by a dichotomous variable: “Poor Neurological Outcome” (CPC 3–5) when assessing “Highly Malignant” EEG patterns and “Malignant” EEG patterns and “Good Neurological Recovery” (CPC 1–2) when assessing “Benign” EEG patterns.

3.8.2. Secondary outcome

The secondary outcome was death (CPC5) when assessing “Highly Malignant” EEG patterns.

3.9. Statistical Analysis

All statistical analyses were performed using software IBM SPSS for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

Baseline and clinical characteristics of categorical variables are presented as the total number of patients (n) and the proportion of patients (%). Continuous variables are reported as the mean and standard deviation (SD).

In bivariate analysis we used the chi-square test for categorical variables and t-test for continuous variables. The level of significance was established at $\alpha<0.05$ (two-tailed). The sensitivity and specificity of EEG patterns to predict poor neurological outcome and death was calculated.

Aiming a robust model to predict secondary outcome, we used a logistic regression model. The variable with a significant association in the bivariate analyses, “Highly Malignant” EEG patterns, was adjusted for possible confounding factors (age >50,

previous mRS >3 and realization of TTM protocol). Specificity and Sensibility was calculated. Confidence Intervals (CI) at 95% and p-values were calculated.

4- Results

4.1. Cohort description

Between January 2014 and August 2018, 248 patients were identified through EEG requisitions (Figure 2). Among this initial group, only 106 patients were eligible for our analysis and 132 patients were excluded: 88 patients underwent EEG outside the time window pre-defined (48 to 100 hours post-CA); 42 patients belonged to other intensive care units, and 2 patients didn´t have enough data available for this study.

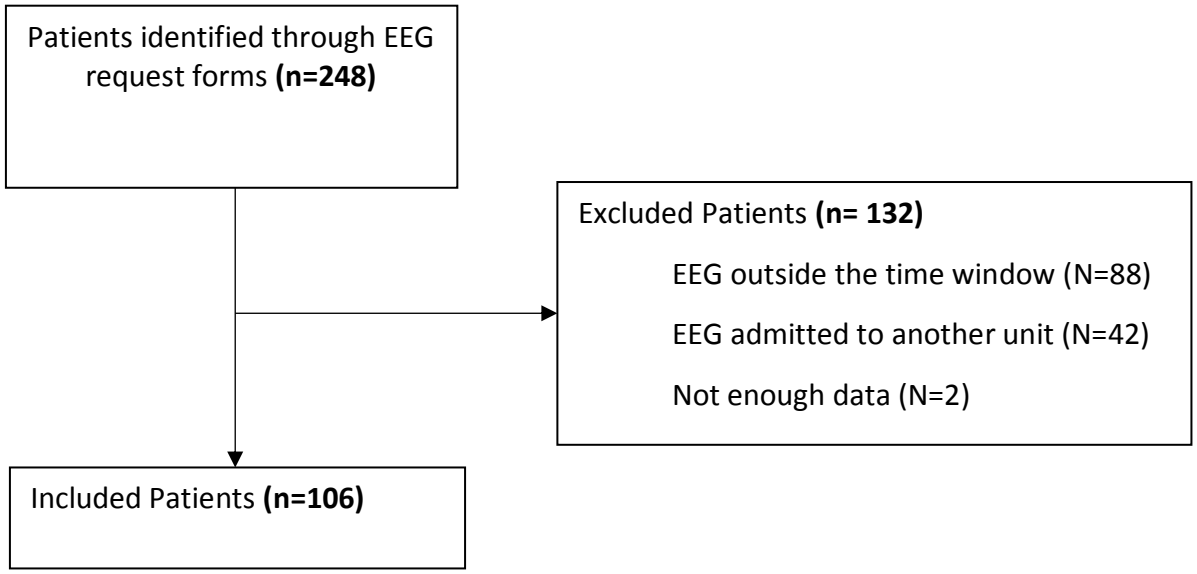

Figure 2. Included/Excluded patients

4.1.1. Patient´s characteristics

Patients included for analysis had a mean age of 62 (±13.9) years old. The youngest patient was 29 years old and the oldest patient was 85 years old. In our cohort, 17 (16.9%) patients had a functional dependency (mRS≥3), prior to CA. Baseline patient´s characteristics are described in table 1.

Table 1 - Baseline patient´s characteristics

All included patients (n=106)	
Patient´s characteristics	
Age y, mean, ± SD	62±13.9
Age >50 y, n (%)	82 (77.4)
Male, n (%)	76 (71.6)
Previous mRS ≥3, n (%)	17 (16.0)
n-number of patients; Y-years; SD- standard deviation; mRS-Modified Rankin-Scale	

The most common cause of cardiac arrest was acute myocardial infarction, present in 37 (34.9%) patients. Table 2 describes Cardiac Arrest etiology.

Table 2– Cardiac arrest etiology

All included patients (n=106)	
CA Cause	
Airway obstruction (%)	8 (7,5)
Acute Myocardial Infarction (%)	37 (34,9)
Aortic Stenosis (%)	1 (0,9)
Acute Pulmonary Edema (%)	1 (0,9)
Disritmia (%)	11 (10,4)
Hemorrhagic Shock (%)	2 (1,9)
Hipoxemia (%)	9 (8,5)
Myocardiopathy (%)	1 (0,9)
Myocarditis (%)	1 (0,9)
Pulmonary Embolism (%)	2 (1,9)
Septic Shock (%)	2 (1,9)
U/N (%)	31 (29,2)
n-number of patients; U/N-unknown	

4.1.2. Patient´s Management

Regarding TTM protocol, 95 (86.6%) patients followed TTM protocol, 43 (40.6%) at 33ºC and 52 (49.1%) at 36ºC, 11 (10.4%) patients did not follow any TTM protocol. A routine EEG was recorded at a mean time of 71 (±15.8) hours (interquartile range 48-100). During EEG recording, 85 (80.2%) patients were under sedation. Data corresponding to patient management is described on table 3.

Table 3–Patient´s Management

All included patients (n=106)	
Patients Management	
In Hospital Cardiac Arrest	31 (29.1)
GCS3 at 72h, n (%)	83 (78.3)
TTM protocol (%)	95 (86.6)
TTM at 33º C, n (%)	43 (40.6)
TTM at 36º C, n (%)	52 (49.1)
Time to EEG hours, mean± SD	71.8 ±15.8
Sedation during EEG*, n (%)	85 (80.2)

n-number of patients; GCS-Glasgow Coma Scale; TTM-Target Temperature Management, EEG - Electroencephalogram; *Sedation in defined as the presence of any of those sedative drugs (midazolam, propofol or fentanyl) during EEG recording.

4.2. EEG results

From the 106 EEG recordings included in our analyses, 37 (34.9%) showed a “Highly Malignant” EEG pattern, 39 (36.8%) showed a “Malignant” EEG Pattern and 30 (28.3%) presented a “Benign” EEG pattern. The description of EEG patterns and subgroups as defined in the methodology is presented in table 4.

Table 4 - EEG pattern description

All included patients (n=106)	
"Highly Malignant" EEG patterns, n (%)	**37 (34.9%)**
Suppressed Background, n	17
Suppressed Background with continuous PD, n	13
Burst-Suppression Background, n	7
"Malignant" EEG patterns, n (%)	**39 (36.8%)**
Abundant rhythmic or periodic pattern, n	14
Abundant SW discharges, n	1
Discontinuous background, n	7
Low voltage background, n	20
Reversed Anterior-Posterior gradient, n	2
Unreactive background, or reactive, only in SIRPIDS, n	18
"Benign" EEG Patterns, n (%)	**30 (28.3%)**
n-number of patients; SW-Spike and Wave or Sharp and Wave Discharge	

4.2.1. Time to EEG and EEG patterns

The mean time between CA and EEG recording was 78.8±15.8 and no differences were found between patients with different EEG patterns (*p-value* = 0.984). Table 5 describes this analysis.

Table 5 - Time to EEG and EEG patterns

	"Highly Malignant" EEG pattern n=37	**"Malignant" EEG pattern n=39**	**"Benign" EEG pattern n=30**	**p-Value**
Time to EEG (± SD)	72.0 ± 16.7	72.8 ± 15.7	71.6 ± 15.5	0.984
SD-Standard Deviation; n-number of patients				

4.2.2. TTM and EEG patterns

The TTM was performed in 95 (89.6%) patients and no differences were found between patients with different EEG patterns (*p-value* = 0.744). Table 6 describes this assay.

Table 6–Realization of TTM protocol and EEG patterns

	"Highly Malignant" EEG pattern n=37	**"Malignant" EEG pattern n=39**	**"Benign" EEG pattern n=30**	**p-Value**
TTM (%)	33 (89.2%)	36 (92.3%)	26 (86.7%)	0.744
TTM-Target Temperature Management; n-number of patients				

4.2.3. Sedation and EEG patterns

85 (80.2%) patients were under sedation during EEG recording and no differences were found between patients with different EEG patterns (*p-value* = 0.989). Table 7 describes the presence of sedation and EEG patterns.

Table 7 - Sedation and EEG patterns

	"Highly Malignant" EEG pattern n=37	**"Malignant" EEG pattern n=39**	**"Benign" EEG pattern n=30**	**p-Value**
Sedation during EEG, n (%)	30 (81.1%)	31 (79,5%)	24 (80,0%)	0.989
n-number of patients; EEG-Electroencephalogram				

4.3. Patient´s outcome

180 days post-CA, patient assessment revealed that 79 (74.5%) had a poor neurological outcome (CPC3-5) and 27 (25.4%) had a good neurological recovery (CPC1-2). Patients´ characteristics and management were not different between outcome groups. Table 8 presents analyzed variables between groups and p-values.

Table 8 - Comparison of patients´ characteristics and management between outcome groups

Variables	**Good neurological recovery (CPC 1-2)**	**Poor neurological outcome (CPC 3-5)**	**p-Value**
Age, mean (± SD)	61.15 (13.60)	62.80 (14.70)	0.595
Age >50	18/27 (66.7%)	61/79 (77.2%)	0.952
Male Gender	20/27 (74.1%)	56/79 (70.9%)	0.751
In hospital Cardiac arrest	4/27 (14.8%)	27/79 (34.2%)	0.056
TTM (33^{o}C or 36^{o}C)	24/27 (88.9%)	71/79 (89.9%)	0.885
Sedation	24/27 (88.9%)	61/79 (77.2%)	0.189
Previous mRS ≥3	3/27 (11.1%)	14/79 (17.7%)	0.419
GCS3 at 72 h	23/27 (85.2%)	60/79 (61.9%)	0.315
Time to EEG, mean (± SD)	71.99 (15.41)	71.42 (16.70)	0.838

SD-Standard Deviation; CPC-Cerebral Performance Category scale; TTM-Target Temperature Management; EEG Electroencephalogram; n-number of patients; mRS - Modified Rankin-Scale

4.3.1. "Highly Malignant" EEG patterns and patients´ outcome

All patients that presented a "Highly Malignant" EEG pattern had a poor neurological outcome [specificity 100% (CI 95% 87.2%-100%) and sensitivity 46.8% (CI 95% 35.5%-58.40%)].

The distribution of the "Highly Malignant" EEG patterns by the patient´s outcome groups is presented in table 9.

Annex I shows some examples "Highly Malignant" EEG patterns.

Table 9 - "Highly Malignant" EEG patterns and patient´s outcome

EEG description	No. (%) (n= 106)	Poor Neurological Outcome (CPC 3-5)	Good Neurological Recovery (CPC 1-2)	p-Value*
At least 1 "Highly Malignant" EEG pattern	**37 (34.9%)**	**37 (100%)**	**0 (0%)**	**--**
Suppressed Background	17 (16.1%)	17 (100%)	0	--
Suppressed Background with continuous PD	13 (12.3%)	13 (100%)	0	--
Burst-Suppression Background	7 (6.6%)	7 100%)	0	--

EEG- Electroencephalogram; n-number of patients; PD- Periodic Discharges

*Bivariate analysis was not possible to perform as there is no patient in good neurological recovery group.

4.3.2. "Malignant" EEG patterns and patients´ outcome

In the "Malignant" EEG pattern group, 29 (74.4%) presented a poor neurological outcome [sensitivity 63.0% (CI 95% 42.4%-80.6%) and specificity 36.7% (CI 95% 26.1%-48.3%)]. The presence of a "Malignant" EEG pattern was not associated with a poor neurological outcome (p-Value=0.976).

The distribution of the "Malignant" EEG patterns by outcome groups is presented in table 10.

Annex II shows some examples "Malignant" EEG patterns.

Table 10 - "Malignant" EEG patterns and patients´ outcome

EEG description	No. (%) (n= 106)	Poor Neurological Outcome (CPC 3-5)	Good Neurological Recovery (CPC 1-2)	*p*-Value
"Malignant" EEG pattern ≥1	**39 (36.8%)**	**29 (74.4%)**	**10 (25.6%)**	**0.976**
"Malignant" EEG patterns ≥2	**18 (17.0%)**	**16 (88.9%)**	**2 (11.1%)**	**0.125**
Abundant rhythmic or periodic pattern	14 (13.2%)	9 (64.3%)	5 (35.7%)	--
Abundant SW discharges	1 (1.0%)	0 (0%)	1 (100%)	--
Discontinuous background	7 (6.6%)	4 (57.1%)	3 (42.9%)	--
Low voltage background	17 (16.0%)	15 (88.2%)	2 (11.8%)	--
Reversed Anterior-Posterior gradient	3 (2.8%)	3 (100%)	0 (0%)	--
Unreactive background, or reactive only in SIRPIDs	18 (17.0%)	15 (83.3%)	3 (16.7%)	--

SIRPIDS-Stimulus Induced Rhythmic Periodic Ictal Discharges; SW-Spike and- Wave or Sharp-and-Wave Discharge

4.3.3. "Benign" EEG patterns and patients´ outcome

Among the patients who presented a "Benign" EEG pattern, 17 (56.7%) showed a good neurological recovery [sensitivity 63.0% (42.4%-80.6%) and specificity 83.5% (73.5%-90.9%)]. The presence of a "Benign" EEG pattern was associated with a Good Neurological recovery (p-Value<0.0001).

The distribution of the benign among patient´s outcome groups is presented in table 11.

Annex III shows an example of a "Benign" EEG pattern.

Table 11-Distribution of Benign EEG and patient´s outcome

EEG description	No. (%) (n= 106)	Poor Neurological Outcome (CPC 3-5)	Good Neurological Recovery (CPC 1-2)	p-Value
"Benign" EEG pattern	**30 (28.3%)**	**13 (43.3%)**	**17 (56.7%)**	**0.000**
EEG-Electroencephalogram; n-number of patients; PD-Periodic Discharges				

Post-Hoc Analysis

At least two malignant characteristics were present simultaneously in 18 patients, of which 16 (88.9%) had a poor neurological outcome [sensitivity 20.3% (12.0%-30.8%) and specificity 92.6% (CI 95% 75.7%-99.1]. The presence of at least two malignant characteristics was not associated with poor neurological outcome (*p*-Value=0.125).

4.3.4. "Highly Malignant" EEG patterns and "death" (*Post-Hoc Analysis*)

180 days post-Cardiac Arrest, 70 (66.1%) patients were dead (CPC5) and 36 (34.0%) patients survived (CPC1-4). Comparing patients´ characteristics and management, no statistically significant difference was found between the patients who did not survive (CPC5) and survivors (CPC1-4), for the majority of variables studied (table 12). However, in our cohort in-hospital cardiac arrest patients show higher mortality (p-value=0.013). These analyses are presented in Table 12.

Table 12- Comparison of patient´s characteristics and management between vital outcome groups

Variables	Dead (CPC 5)	Alive (CPC 1-4)	p-Value
Mean age (± SD)	63.23 (14.18)	60.72 (13.14)	0.379
Age >50	54/70 (77.1%)	28/36 (77.8%)	0.941
Male Gender	50/70 (71.4%)	26/36 (72.2%)	0.932
In hospital Cardiac Arrest	26/70 (37.1%)	5/36 (13.8%)	**0.013**
TTM (33° or 36°)	65/70 (92.9%)	30/36 (83.3%)	0.128
Sedation	55/70 (78.6%)	30/36 (83.3%)	0.560
Previous mRS ≥3	14/70 (20.0%)	3/36 (8.3%)	0.121
3 on GCS at 72h	53/70 (75.7%)	30/36 (83.3%)	0.367

SD-Standard Deviation; CPC-Cerebral Performance Category scale; TTM-Target Temperature Management; EEG-Electroencephalogram; n-number of patients; mRS-Modified Rankin-Scale; GCS-Glasgow Coma Scale

From the 37 patients with a "Highly Malignant" EEG pattern, 32 (86.5%) died, in the first 6 months after Cardiac Arrest [sensitivity 45.7% (33.7%-58.1%) and specificity 86.1% (70.5%-95.3%)]. The presence of a "Highly Malignant" EEG pattern is associated with death (p-Value=0.001). The distribution of the "Highly Malignant" EEG patterns by the outcome groups is presented in table 13.

Table 13- Distribution of "Highly Malignant" EEG patterns by vital outcome groups

EEG description	No. (%) (n= 106)	Dead	Survive	p-Value
"Highly Malignant"	**37 (34.9%)**	**32 (86.5%)**	**5 (13.5%)**	**0.001**
Suppressed Background	17 (16.1%)	14 (82.4%)	3 (17.6%)	--
Suppressed Background with continuous PD	13 (12.3%)	11 (84.6%)	2 (15.4%)	--
Burst-Suppression Background	7 (6.6%)	7 (100%)	0 (0%)	--

EEG-Electroencephalogram; n-number of patients; PD-Periodic Discharges

In the multivariate analysis, after adjustment for possible confounders (age >50, previous mRS>3 and realization of TTM protocol), “Highly Malignant” EEG pattern remain independent predictors of death [p=0.001, OR=6.59 (IC95% 2.17-20.01)]. The percentage accuracy in classification (PAC) of the constructed model was 67%. Further model characteristics are showed in table 14. The discriminative capacity of this model was poor with an area under the ROC (Receiver Operating Characteristic) curve of 65.9%. Figure 3 represents the ROC curve.

Table 14. Characteristics of the multimodal prediction model

	Omnibus test	Cox & Snell R^2	Nagelkerke R^2	Hosmer and Lemeshow Test	Odds Ratio	PAC	AUC	Sensitivity	Specificity	PPV	NPV
Value (CI 95%)	0.001	0.163	0.226	0.771	6.581 (2.165-20.006)	67.0% (57.2-75.8%)	0.659 (0.554-0.765)	8.3% (1.8-22.5%)	97.1% (90.1-99.7%)	60.0% (20.8-89.6%)	67.3% (65.0-69.6%)

CI- Confidence Intervals; PPV-Positive Predictive Value; NPV-Negative Predictive Value; PAC-Percentage Accuracy in Classification; AUC-Area Under the Curve

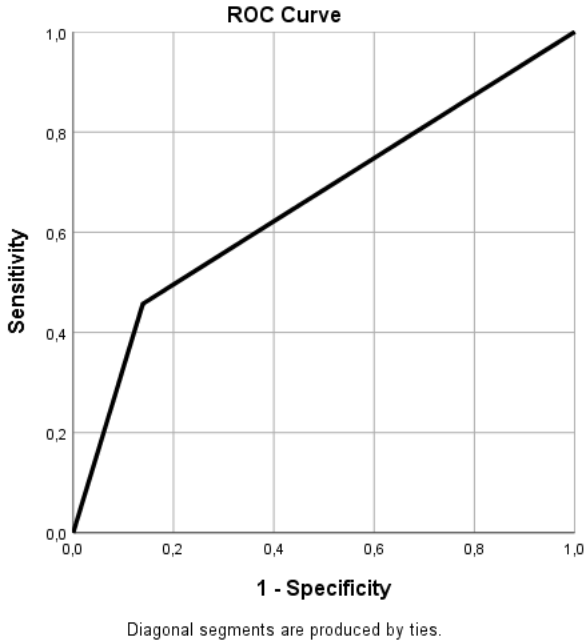

Figure 3. The receiver operating characteristic (ROC) curve

5. Discussion

5.1- Data Discussion

In this study, 34.9% of patients had a “Highly Malignant” EEG pattern and all post-cardiac arrest patients with this neurophysiological characteristic had a poor neurological outcome. Furthermore, this EEG pattern was independently associated with dead. Therefore, we documented the importance of a standardized EEG analysis in the assessment of post-cardiac arrest prognosis.

As postulated, our results are in line with Westhall and collaborators (Westhall et al., 2016) findings. These authors previously found that “Highly Malignant” EEG patterns predict an unfavorable outcome in half of their patients, with no false positives. Furthermore, in both series (our and Westhall et al., 2016), this EEG pattern showed a limited sensitivity (46.8% in our series) for identifying poor neurological outcome. Many patients with poor neurological outcome did not present any EEG characteristic from the “Highly Malignant” pattern group. Although other factors can account for this observation, such as medical complications during admission or comorbidities, is it possible to speculate that other EEG patterns (not included in “Highly Malignant” group) and other variables might also be associated with poor neurological outcome.

Although we found a high specificity to the “Highly Malignant” pattern group, a very recent study (Beuchat et al., 2018), showed a slightly lower specificity 91% (95% CI: 83%–97%). However, they scored EEGs performed in the first 24 hours when the patients still under sedation and this can account for the few false positives that they found. This reinforce the recommendation of prognostication 3-5 days after CA from the European guidelines (Sandroni et al., 2014).

In the *post-hoc* analysis, “Highly Malignant” EEG patterns were predictors of a more severe outcome: death. In fact, the odds for dying was 6.5 times higher when at least one of “Highly Malignant” EEG feature was present. Although, we could corroborate an association independently from age, previous functional status and TTM protocol, the characteristics of the prediction model showed that only 60% of patients with this EEG pattern will die (with a wide confidence interval) and almost 70% of patients

without this EEG pattern will survive. Indeed, even after controlling for possible confounding variables, the discriminative capacity of the logistic regression model for predicting dead was poor. These observations disclose once again the decision difficulty of withdrawing life sustaining treatment in post-CA patients (Callaway 2018) and how important it is to avoid self-fulfilling prophecies. Furthermore, it points to the urgent need of improve post cardiac arrest prognostication. Multimodal evaluation including EEG in combination with neurological examination and other ancillary tests might be the answer and should be explored in a standardized way in future studies.

Other EEG characteristics were also evaluated in our study as possible prognostic markers. “Malignant” EEG patterns were presented in almost 40% of our patients but the presence of at least one of these characteristics was not associated with poor neurological outcome. These findings are also consistent with Westhall and collaborators (Westhall et al., 2016). However, we could not support these authors findings of an association between the presence of at least two malignant characteristics with poor neurological outcome.

Regarding specific characteristics from the “Malignant” EEG pattern group, EEG reactivity deserves close observation. Our results show that almost 17% of patients with unreactive EEG or EEG only reactive with SIRPIDS had a good neurological recovery. Therefore, this characteristic is not always associated with poor neurological outcome as previously stated (Crepeau et al., 2013, Oddo et al., 2012, Rossetti et al., 2014). In fact, Bouwes and collaborators (Bouwes et al., 2012) previously described in their study three patients without EEG reactivity after rewarming which had a favorable outcome. This discrepancy might also be related with the interpretation problems associated with EEG reactivity. Recently, it has been demonstrated that even among experts, agreement in EEG interpretation is only fair for reactivity findings (Westhall et al., 2015).

Another important EEG feature deserving our comment is the presence of abundant rhythmic and periodic patterns in 13% of our patients. It is known that these patterns might be related with an ictal state and status epilepticus (Beniczky et al, 2013; Leitinger et al., 2015; Osman et al., 2018) or an ictal-interictal continuous state (Osman

et al., 2018). More than 1/3 of our patients with this EEG pattern had a good neurological recovery. Although status epilepticus has been associated with poor neurological outcome in post cardiac arrest patients (Sandroni et al., 2014), the percentage of patients fulfilling status epilepticus criteria was not quantified in our series. Also, it is not clear whether treating status epilepticus nor even rhythmic and periodic patters not fulfilling status epilepticus criteria prevents additional brain damage and improve outcome. However, our results suggest that recovery can occur in a significant percentage of these patients and argues in favor of their intensive treatment until recovery or until other predictors of a poor neurological outcome arise, as proposed by Elmer and collaborators in 2016 (Elmer et al., 2016).

Another interesting feature of our work was the evaluation of "Benign" EEG patterns as possible good prognostic biomarkers after cardiac arrest. Even though, 55.7% of patients with this EEG feature showed a good neurological recovery, this is a lower percentage compared to Westhall et al. study (93%) (Westhall et al., 2016). This is possibly justified by the difference in definition of outcome. In westhall series, they consider the best scored achieved in 6 months, as it is a prospective study, and we considered the score at 6 months, which justifies the difference and compromises the comparison.

5.2- Strengths and weaknesses of this study

One strength of this study was its multicentric design. Our Lisbon collaborative analysis with access both to clinical and neurophysiological data from two different central hospitals provided peer and interdisciplinary discussion, active learning and a large and representative sample, with an effect in the credibility of our results and the power of statistical analysis. Other strengths of our study are some methodological features. The use of ACNS EEG terminology to Intensive Care provides standardization between investigators and previous studies. The analyses of the EEG recording in a specific time window also allowed comparison with previous scientific evidence and the use of a multimodal predictor model of death the adjustment for some possible confounder variables.

The weakness of this study is its retrospective nature that compromised some quality of our data and made access to other important information very difficult. In order to comprehensively evaluate post cardiac arrest prognostic other well-known outcome biomarkers should be included in the prognostication, such as MRI characteristic's, brainstem reflexes (especially corneal and pupillary reflexes), the presence of shockable rhythms and SSEP. Furthermore, our retrospective sample was a convenience sample, a larger sample will increase the power of the analysis, minimizing error type II.

Other limitation of our study was the fact that we also didn´t have access to the cause of patient´s death, which may be related with other conditions different from hypoxic brain injury.

5.3- Future Directions

This study adds clinical evidence to the current clinical practice of requesting an EEG in the prognostication of cardiac arrest patients. It also reinforces that EEG must not be taken by itself in this outcome prediction.

Moreover, the accuracy of a prognostic model can be improved. In the future, it would be useful to replicate this study in a prospective way, combining other clinical, neurophysiological and ancillary tests predictors and including other Intensive Care Units and/or Hospitals. This would allow access to larger samples and to subgroup analyses. Also, other EEG analysis such as quantitative EEG can be explored as biomarkers in this prognostication. And investigate the better type of EEG recording (continuous vs spot EEG) as it remains to be defined for prediction. The effect of status epilepticus and its treatment in the outcome of post cardiac arrest patients is also an important research topic.

It would also be important to compare series in a systematic review and metanalysis of the few studies with similar protocols that have been recently published.

6- Conclusions highlights

In our cohort of post cardiac arrest patients,

- “Highly Malignant” EEG patterns were associated with poor neurological outcome.
- “Highly Malignant” EEG patterns were independent predictors of dead.
- “Malignant” EEG patterns were not associated with a poor neurological outcome.
- “Benign” EEG patterns were associated with good neurological recovery.

Overall, this study increased the knowledge about the value of EEG as a diagnostic tool in outcome prediction of patients after cardiac arrest. A comprehensive, multimodal, standardized and multicentric approach to post cardiac arrest prognostication is recommended.

7- References

Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. *European Heart Journal*. 2006;27(23):2840-2845. doi:10.1093/eurheartj/ehl335

Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin Scale: implications for stroke clinical trials—a literature review and synthesis. *Stroke* 2007;38:1091–1096.

Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. *Epilepsia*. 2013;54:28-29. doi:10.1111/epi.12270

Beuchat I, Solari D, Novy J, Oddo M, Rossetti AO. Standardized EEG interpretation in patients after cardiac arrest: Correlation with other prognostic predictors. *Resuscitation*. 2018;126:143-146. doi:10.1016/j.resuscitation.2018.03.012

Bigham S, Bigham C, Martin D. Predictors of Outcome Post Cardiac Arrest. *Journal of Intensive Care Medicine*. 2018;33(4):248-255. doi:10.1177/0885066613511045

Bouwes A, van Poppelen D, Koelman JH, et al. Acute posthypoxic myoclonus after cardiopulmonary resuscitation. *BMC neurology*. 2012;12(1):63.

Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post–Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 suppl 2):S465-S482. doi:10.1161/CIR.0000000000000262

Callaway CW. Neuroprognostication postcardiac arrest: translating probabilities to individuals. *Current Opinion in Critical Care*. 2018;24(3):158-164. doi:10.1097/MCC.0000000000000500

Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for Refractory Status

Epilepticus. *Neurocritical Care*. 2008;9(2):189-197. doi:10.1007/s12028-008-9092-9

Crepeau AZ, Britton JW, Fugate JE, Rabinstein AA, Wijdicks EF. Electroencephalography in Survivors of Cardiac Arrest: Comparing Pre- and Post-therapeutic Hypothermia Eras. *Neurocritical Care*. 2015;22(1):165-172. doi:10.1007/s12028-014-0018-4

Crepeau AZ, Rabinstein AA. Continuous EEG in therapeutic hypothermia after cardiac arrest. 2013:7.

Dell'Anna AM. Acute kidney injury after cardiac arrest: a systematic review and meta-analysis of clinical studies. *Minerva Anestesiologica*. 2016;82(9):16.

Dragancea I, Horn J, Kuiper M, et al. Neurological prognostication after cardiac arrest and targeted temperature management 33°C versus 36°C: Results from a randomised controlled clinical trial. *Resuscitation*. 2015;93:164-170. doi:10.1016/j.resuscitation.2015.04.013

Elmer J, Rittenberger JC, Faro J, et al. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest: EEG Phenotypes of PAMM. *Annals of Neurology*. 2016;80(2):175-184. doi:10.1002/ana.24697

Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. *Resuscitation*. 2016;102:127-135. doi:10.1016/j.resuscitation.2016.01.016

Friberg H, Cronberg T, Dünser MW, Duranteau J, Horn J, Oddo M. Survey on current practices for neurological prognostication after cardiac arrest. *Resuscitation*. 2015;90:158-162. doi:10.1016/j.resuscitation.2015.01.018

Fugate JE, Brinjikji W, Mandrekar JN, et al. Post–Cardiac Arrest Mortality Is Declining: A Study of the US National Inpatient Sample 2001 to 2009. *Circulation*. 2012;126(5):546-550. doi:10.1161/CIRCULATIONAHA.111.088807

Fugate JE, Wijdicks EFM, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. *Annals of Neurology*. 2010;68(6):907-914. doi:10.1002/ana.22133

Gaspard N, Hirsch LJ, LaRoche SM, Hahn CD, Westover MB, the Critical Care EEG Monitoring Research Consortium. Interrater agreement for Critical Care EEG Terminology. *Epilepsia*. 2014;55(9):1366-1373. doi:10.1111/epi.12653

Guilliams K, Rosen M, Buttram S, et al. Hypothermia for pediatric refractory status epilepticus. *Epilepsia*. 2013;54(9):1586-1594. doi:10.1111/epi.12331

Guluma KZ, Oh H, Yu S-W, Meyer BC, Rapp K, Lyden PD. Effect of Endovascular Hypothermia on Acute Ischemic Edema: Morphometric Analysis of the ICTuS Trial. *Neurocritical Care*. 2008;8(1):42-47. doi:10.1007/s12028-007-9009-z

Herlitz J, Engdahl J, Svensson L, Ängquist K-A, Young M, Holmberg S. Factors associated with an increased chance of survival among patients suffering from an out-of-hospital cardiac arrest in a national perspective in Sweden. *American Heart Journal*. 2005;149(1):61-66. doi:10.1016/j.ahj.2004.07.014

Herlitz J. Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Goteborg, Sweden. *Heart*. 2003;89(1):25-30. doi:10.1136/heart.89.1.25

Hirsch LJ, LaRoche SM, Gaspard N, et al. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version. *Journal of Clinical Neurophysiology*. 2013;30(1):1–27.

Hofmeijer J, van Putten MJAM. Ischemic Cerebral Damage: An Appraisal of Synaptic Failure. *Stroke*. 2012;43(2):607-615. doi:10.1161/STROKEAHA.111.632943

Hollenberg J, Herlitz J, Lindqvist J, et al. Improved Survival After Out-of-Hospital Cardiac Arrest Is Associated With an Increase in Proportion of Emergency Crew–Witnessed Cases and Bystander Cardiopulmonary Resuscitation. *Circulation*.

2008;118(4):389-396. doi:10.1161/CIRCULATIONAHA.107.734137

Hovdenes J, Røysland K, Nielsen N, et al. A low body temperature on arrival at hospital following out-of-hospital-cardiac-arrest is associated with increased mortality in the TTM-study. *Resuscitation*. 2016;107:102-106. doi:10.1016/j.resuscitation.2016.08.011

Kjaergaard J, Nielsen N, Winther-Jensen M, et al. Impact of time to return of spontaneous circulation on neuroprotective effect of targeted temperature management at 33 or 36 degrees in comatose survivors of out-of hospital cardiac arrest. *Resuscitation*. 2015;96:310-316. doi:10.1016/j.resuscitation.2015.06.021

Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP. Predicting survival from out-of-hospital cardiac arrest: A graphic model. *Annals of Emergency Medicine*. 1993;22(11):1652-1658. doi:10.1016/S0196-0644(05)81302-2

Leitinger M, Beniczky S, Rohracher A, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus – approach to clinical application. *Epilepsy & Behavior*. 2015;49:158-163. doi:10.1016/j.yebeh.2015.05.007

Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Medicine*. 2013;39(11):1972-1980. doi:10.1007/s00134-013-3043-4

Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. *Resuscitation*. 2014;85(6):732-740. doi:10.1016/j.resuscitation.2014.03.008

Lybeck A, Friberg H, Aneman A, et al. Prognostic significance of clinical seizures after cardiac arrest and target temperature management. *Resuscitation*. 2017;114:146-151. doi:10.1016/j.resuscitation.2017.01.017

Maupain C, Bougouin W, Lamhaut L, et al. The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. *European Heart Journal*. 2016;37(42):3222-3228. doi:10.1093/eurheartj/ehv556

Mikhaeil-Demo Y, Gavvala JR, Bellinski II, et al. Clinical classification of post anoxic myoclonic status. *Resuscitation*. 2017;119:76-80. doi:10.1016/j.resuscitation.2017.07.035

Morrison LJ, Deakin CD, Morley PT, et al. Part 8: Advanced Life Support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122(16_suppl_2):S345-S421. doi:10.1161/CIRCULATIONAHA.110.971051

Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiologica Scandinavica*. 2009;53(7):926-934. doi:10.1111/j.1399-6576.2009.02021.x

Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *New England Journal of Medicine*. 2013;369(23):2197-2206. doi:10.1056/NEJMoa1310519

Oddo M, Crippa IA, Mehta S, et al. Optimizing sedation in patients with acute brain injury. *Critical Care*. 2016;20(1):128. doi:10.1186/s13054-016-1294-5

Oddo M, Friberg H. Neuroprognostication after cardiac arrest in the light of targeted temperature management: *Current Opinion in Critical Care*. 2017;23(3):244-250. doi:10.1097/MCC.0000000000000406

Osman GM, Araújo DF, Maciel CB. Ictal Interictal Continuum Patterns. *Current Treatment Options in Neurology*. 2018;20(5). doi:10.1007/s11940-018-0500-y

Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18_suppl_3):S768-S786. doi:10.1161/CIRCULATIONAHA.110.971002

Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of

the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. :16.

Rossetti AO, Bleck TP. What's new in status epilepticus? *Intensive Care Med*. 2014;40(9):1359-1362. doi:10.1007/s00134-014-3363-z

Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: A prospective study. *Annals of Neurology*. 2010:NA-NA. doi:10.1002/ana.21984

Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: An advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Intensive Care Medicine*. 2014;40(12):1816-1831. doi:10.1007/s00134-014-3470-x

Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. *Resuscitation*. 2013;84(10):1324-1338. doi:10.1016/j.resuscitation.2013.06.020

Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of Survival From Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis. *Circulation: Cardiovascular Quality and Outcomes*. 2010;3(1):63-81. doi:10.1161/CIRCOUTCOMES.109.889576

Shinozaki K, Oda S, Sadahiro T, et al. Blood ammonia and lactate levels on hospital arrival as a predictive biomarker in patients with out-of-hospital cardiac arrest. *Resuscitation*. 2011;82(4):404-409. doi:10.1016/j.resuscitation.2010.10.026

Sivaraju A, Gilmore EJ, Wira CR, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. *Intensive Care Medicine*. 2015;41(7):1264-1272. doi:10.1007/s00134-015-3834-x

Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation*. 2015;95:100-147.

doi:10.1016/j.resuscitation.2015.07.016

Søholm H, Kjær TW, Kjaergaard J, et al. Prognostic value of electroencephalography (EEG) after out-of-hospital cardiac arrest in successfully resuscitated patients used in daily clinical practice. *Resuscitation*. 2014;85(11):1580-1585. doi:10.1016/j.resuscitation.2014.08.031

Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, et al. Early EEG for outcome prediction of postanoxic coma: prospective cohort study with cost-minimization analysis. *Critical Care*. 2017;21(1). doi:10.1186/s13054-017-1693-2

Spalletti M, Carrai R, Scarpino M, et al. Single electroencephalographic patterns as specific and time-dependent indicators of good and poor outcome after cardiac arrest. *Clinical Neurophysiology*. 2016;127(7):2610-2617. doi:10.1016/j.clinph.2016.04.008

Synek VM. EEG Abnormality Grades and Subdivisions of Prognostic Importance in Traumatic and Anoxic Coma in Adults. *Clinical Electroencephalography*. 1988;19(3):160-166. doi:10.1177/155005948801900310

Taccone FS, Colpaert K, De Waele J, et al. Targeted temperature management and neuroprognostication after cardiac arrest: A survey in Belgium. *Resuscitation*. 2015;96:e1-e2. doi:10.1016/j.resuscitation.2015.08.017

Teasdale et al., ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS: A Practical Scale: *The Lancet.* 1974; Pages 81-84: doi: 10.1016/S0140-6736(74)91639-0

The hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *ACC Current Journal Review*. 2002;11(4):82. doi:10.1016/S1062-1458(02)00735-3

Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJAM. Electroencephalogram Predicts Outcome in Patients With Postanoxic Coma During Mild Therapeutic Hypothermia*: *Critical Care Medicine*. 2015;43(1):159-167. doi:10.1097/CCM.0000000000000626

Uchino H, Ogihara Y, Fukui H, et al. RETRACTED ARTICLE: Brain injury following cardiac arrest: pathophysiology for neurocritical care. *Journal of Intensive Care*. 2016;4(1). doi:10.1186/s40560-016-0140-9

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver Agreement for the Assessment of Handicap in Stroke Patients. :5.

Westhall E, Rosén I, Rossetti AO, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients. *Clinical Neurophysiology*. 2015;126(12):2397-2404. doi:10.1016/j.clinph.2015.03.017

Westhall E, Rossetti AO, van Rootselaar A-F, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology*. 2016;86(16):1482-1490. doi:10.1212/WNL.0000000000002462

Wibrandt I, Norsted K, Schmidt H, Schierbeck J. Predictors for outcome among cardiac arrest patients: the importance of initial cardiac arrest rhythm versus time to return of spontaneous circulation, a retrospective cohort study. *BMC Emergency Medicine*. 2015;15(1):3. doi:10.1186/s12873-015-0028-3

Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;67(2):203–210.

Winther-Jensen M, Kjaergaard J, Wanscher M, et al. No difference in mortality between men and women after out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:78-84. doi:10.1016/j.resuscitation.2015.06.030

Wnent J, Masterson S, Gräsner J-T, et al. EuReCa ONE – 27 Nations, ONE Europe, ONE Registry: a prospective observational analysis over one month in 27 resuscitation registries in Europe – the EuReCa ONE study protocol. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*. 2015;23(1):7. doi:10.1186/s13049-015-0093-3

Young GB, McLachlan RS, Kreeft JH, Demelo JD. An Electroencephalographic Classification for Coma. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 1997;24(04):320-325. doi:10.1017/S0317167100032996

Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A. Systematic review of early prediction of poor outcome in anoxicischaemic coma. *The Lancet*. 1998;352(9143):1808-1812. doi:10.1016/S0140-6736(98)04076-8

8- Annexes

Annex I – "Highly Malignant" EEG patterns

Figure 4. Periodic Discharges in a Suppressed Background

Figure 5. Suppressed Background

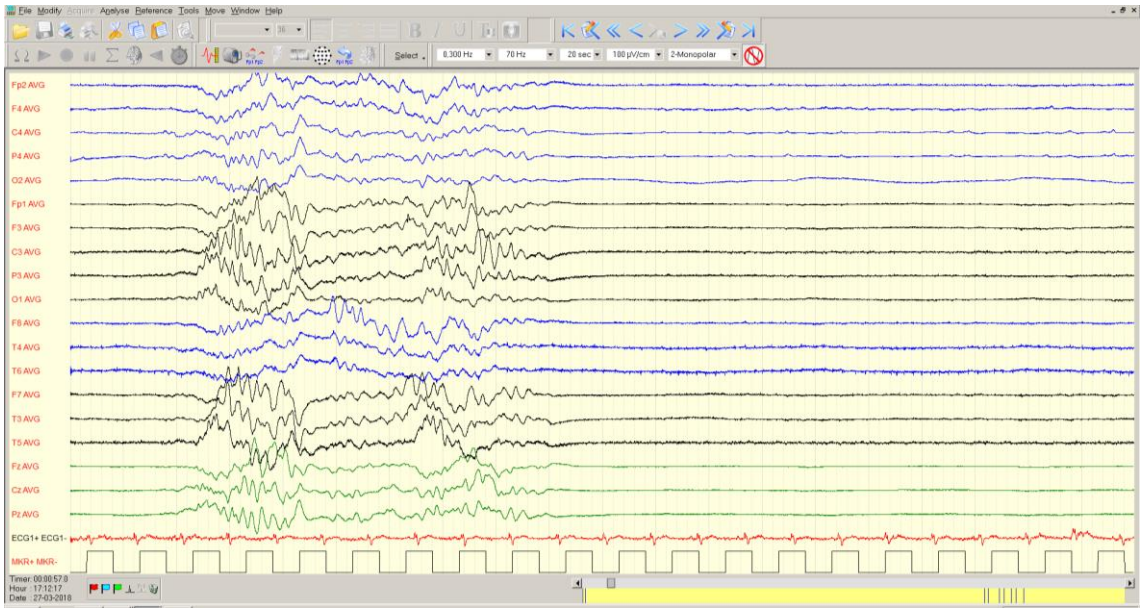

Figure 6. Burst-Supression Background

Annex II – “Malignant” EEG patterns

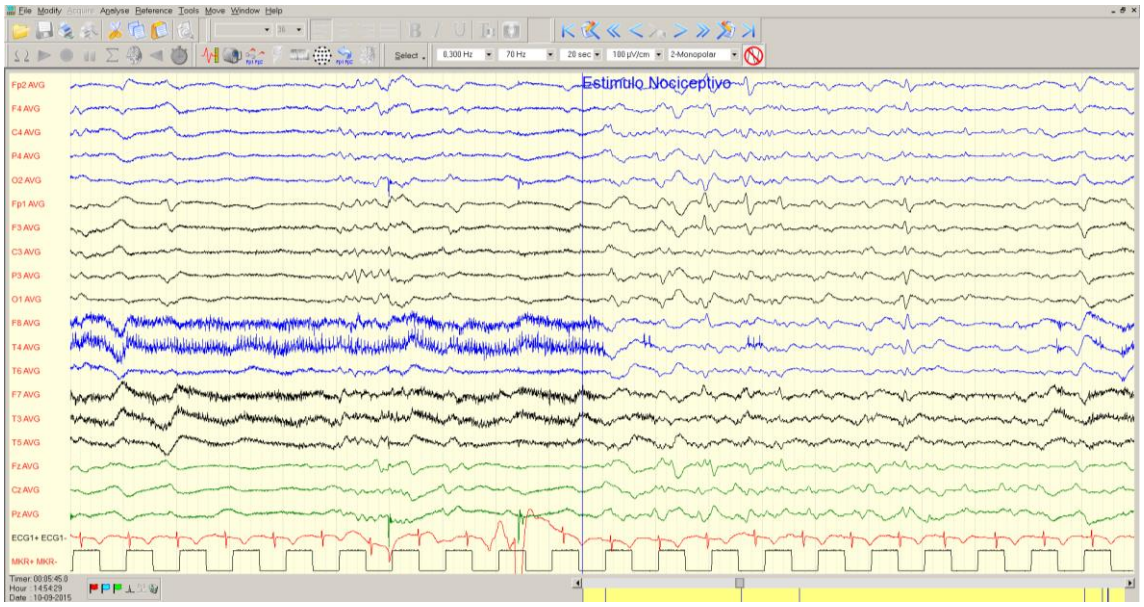

Figure 7. Stimulus Induced Rythmic Periodic Ictal Discharges (SIRPIDs)

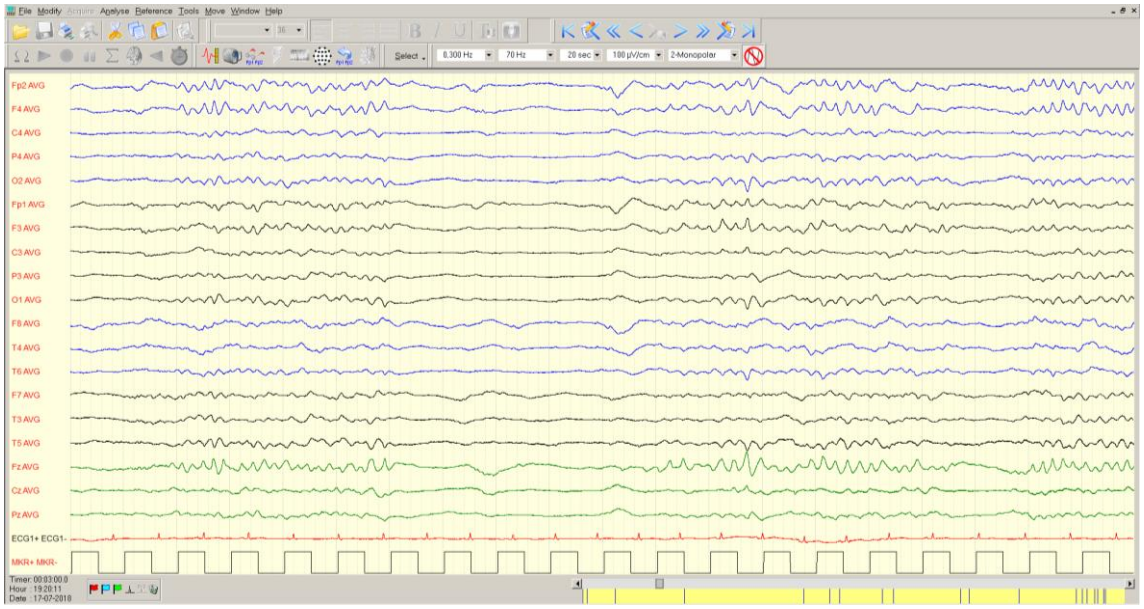

Figure 8. Discontinuous Background

Annex III – “Benign” EEG Pattern

Figure 9. Absence of “Highly Malignant” and “Malignant” features